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(73) AWD.PHARMA GMBH & CO. KG
Leipziger Strasse 7-13,01097 DRESDEN XX (DE).

(72) NICKEL, BERND (DE).
LOBISCH, MICHAEL (DE).
SZELENYI, STEFAN (DE).
ENGEL, JURGEN (DE).
EMIG, PETER (DE).
PERGANDE, GABRIELA (DE).

(74) MARKS & CLERK

(54) PREPARATION COMBINEE CONTENANT DE LA FLUPIRTINE ET DE LA MORPHINE POUR LE TRAITEMENT DES ALGIES ET LA PREVENTION DE LA DEPENDANCE MORPHINIQUE

(54) COMBINATION PREPARATION CONTAINING FLUPIRTIN AND MORPHINE FOR THE TREATMENT OF PAIN AND THE PREVENTION OF MORPHINE DEPENDENCE

(57)

The combination of flupirtin and morphine has the property of having a strong analgesic action and of not causing any morphine-like dependence and tolerance. New medicaments containing this active substance combination are described.

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(72) Inventeurs/Inventors:
NICKEL, BERND, DE;
LOBISCH, MICHAEL, DE;
SZELENYI, STEFAN, DE;
ENGEL, JURGEN, DE;
EMIG, PETER, DE;
PERGANDE, GABRIELA, DE

(73) Propriétaire/Owner:
AWD.PHARMA GMBH & CO. KG, DE

(74) Agent: MARKS & CLERK

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(57) Abrégé/Abstract:
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ABSTRACT OF THE DISCLOSURE

The combination of flupirtin and morphine has the property of having a strong analgesic action and of not causing any morphine-like dependence and tolerance. New medicaments containing this active substance combination are described.

Morphine, which is derived from opium, the dried milky exudate of unripe poppy capsules (Papaver somniferum), has been used in the form of its hydrochloride as an agent against severe pain since its isolation by Sertürner (1806). When this analgesic is used frequently and over a long period of time, for example in tumor patients, there is a risk of addiction and the development of tolerance (morphinism).

The side effects observed during correct use, such as euphoric effect, emetic effect, spastic constipation and increase in smooth musculature tone, also reduce the therapeutic applicability of morphine. There has therefore been no lack of attempts to synthesize strongly acting, but side effect-free analgesics. Although the partially synthetic product diamorphine (heroin) is 10 times more effective than morphine, it leads to addiction much more easily. The action of pethidine is about 5 times weaker effective than morphine and is also less spasmogenic.

Pentazocine and buprenorphine fall within narcotics legislation on account of their addiction potential.

Tramadol is only about 1/10 - 1/5 as effective as morphine, but instead is not yet known to present an addiction potential.

There thus remains a great need for a reliable analgesic medication that is also highly effective in severe pain with few side effects which, for social reasons, should present no addiction potential.

The solution of a combination of active substances has been adopted to reduce the use of analgesics, or to enhance the not always adequate analgesic effect. These attempts have aimed at making the side effects of morphine less pronounced and enhancing the analgesic effect by combining selected analgesics with morphine.

Since morphine has no anti-inflammatory effect, this deficit in the effect of morphine can be balanced out by combining morphine with anti-inflammatory or anti-pyretic analgesics. Thus, for example, Vergoni et al. (Life Sci., 50(16), page 135-138 (1992)) describe the potentiating effects of pinacidil on the analgesic effect of morphine.

A combination of rectally administered indomethacin with intravenously administered morphine is described by Segstro and Morley-Forster in Can. J. Anaesth. 38(5), 578-581 (1991).

Animal experiments which describe the potentiation of analgesic effects of morphine and clonidine in rats were

reported by Wilcox, Carlsson, Jochim and Jurna in Brain Res. 405(1), 84-93 (1987).

All experiments are aimed at enhancing the analgesic effects in the sense of a synergistic effect in order to reduce the dose of analgesic or anti-inflammatory agent and morphine.

Flupirtin (INN) is an analgesic with muscle-relaxing components of action. (B. Nickel, V. Jakovlev, I. Szelenyi, Arzneim.-Forsch. 40(II)8, 909-911 (1990) German published patent 36 01 195).

It has no dependence potential (B. Nickel, H.O. Barbe, I. Szelenyi, Arzneim.-Forsch. 40(II)8, 905-908 (1990)). The antinociceptive effect of flupirtin cannot be antagonized by naloxon. Flupirtin also shows no affinity with opiate receptors. (B. Nickel, A. Herz, V. Jakovlev, U. Tibes, Arzneim.- Forsch. 35(II), 1402 (1985)).

It has now been found that flupirtin, given alone, does not lead to the development of tolerance. It was also surprisingly found that there were no signs of tolerance when the combination of flupirtin and morphine was given. This is unexpected since the structure of flupirtin differs greatly from the known morphine antagonists naloxon or methadone.

The invention provides improved medicaments with an analgesic action that display a greatly reduced addiction potential or even no addiction potential at all.

More specifically, the present invention provides a pharmaceutical composition formulated to deliver to a patient flupirtin or a pharmaceutically acceptable salt thereof in an amount, calculated as a free base, of 5 mg/kg, and a pharmaceutically acceptable salt of morphine in an amount, calculated as a free base, of 2.5 mg/kg to 10 mg/kg, wherein the analgesic effectiveness of the morphine is preserved, and wherein potential for development of dependence on and tolerance to the morphine in the patient is reduced.

The invention will be further described by reference to the accompanying drawings, in which:

Figure 1 describes the development of tolerance over 45 days of combination compared to the individual substances.

Figure 2 shows the antinociceptive effect of the combination compared to the individual substances.

Figure 3 shows the results of a trial on mental dependence.

Figure 4 shows on the basis of the rearing of rats the stimulatory effect of morphine alone and the non-stimulatory effect of the combination of the invention.

Figure 5 shows a similar version as Figure 4: here the path is measured as an indication of the stimulation of the animals.

Figure 6 shows the influence of the individual substances on muscle relaxation compared to the combination

of the invention.

The weights set out in the claims and in the specification always relate to the free bases.

Administration of flupirtin over several weeks did not lead to tolerance in animal experiments. (Figure 1). The analgesic effect was maintained over the entire duration of the experiment (45 days).

The examination was conducted in the electro-pain test in the rat (after Blake et al. Arz. Med. exp. 9, 146 (1963)).

An additive, antinociceptive effect was observed after the single administration of flupirtin in combination with morphine.(Figure 2). The sole administration of flupirtin leads to an antinociceptive effect of 45%, the administration of the combination yields an effect of 100%.

In examining physical dependence the already often described symptom of dependence due to morphine, decrease in animal weight after withdrawal, was significantly relieved by flupirtin in combination with morphine (Figure 3). Flupirtin cancels or weakens the physical dependence potential of morphine.

It may also be assumed that flupirtin cancels or markedly diminishes the dependence and withdrawal symptoms provoked by other combinations such as those of the barbiturate, alcohol, amphetamine, cocaine, cannabis or hallucinogen type.

The test for the possible presence of mental dependence was conducted according to the method of Hosoya, Pharmacol. Meth. Tox, 5, 515 (1979).

The behavior of animals on the day of withdrawal was recorded during the same long-term investigation. It was also found in this model that the behavior of the animals was markedly influenced by flupirtin in the combination after withdrawal of morphine (stimulation, rearing) (Figure 4,5). The marked stimulation or rearing behavior of the animals after morphine is reduced in the combination with flupirtin and rather resembles that of untreated control animals. Flupirtin also relieved the rigidity provoked in animals by morphine. (Figure 6).

In one tablet the medicament contains for example 10 mg to 1000 mg flupirtin in the form of a pharmaceutically acceptable salt and 5 mg to 500 mg morphine in the form of a pharmaceutically acceptable salt and preferably 50 mg - 500 mg flupirtin and 10 mg - 250 mg morphine.

Salt formers that may be considered in the case of flupirtin are for example hydrochloric acid, gluconic acid, malonic acid and maleic acid; in the case of morphine, mineral acids such as hydrochloric acid and sulphuric acid may be considered.

The medicament of the invention may be present in the form of tablets, capsules, pellets, granulates, ampoules for intravenous and intramuscular injection, in the form of infusion solutions and suppositories. The preparation of the medicaments is effected in known manner, known and conventional pharmaceutical auxiliary substances as well as other conventional carriers and dilutants being used.

Carriers and auxiliary substances of this kind that may be used are for example substances recommended or listed in the following literature references as auxiliary substances for pharmaceutical, cosmetic and adjacent fields: Ullmanns Encyklopädie der technischen Chemie, Volume 4 (1953), page 1 to 39; Journal of Pharmaceutical Sciences, Volume 52 (1963), page 918 et seq. H.v.Czetsch-Lindenwald, Hilfsstoffe für Pharmazie und angrenzende Gebiete; Pharm. Ind. Issue 2, 1961, page 72 et seq.; Dr. H.P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, 2nd edition, Editio Cantor, Aulendorf in Württemberg 1981 and Pharmazeutische Technologie (publishers: Fuchs, Sucker, Speiser, Georg Thieme Verlag, 2nd edition (1991).

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A pharmaceutical composition formulated to deliver to a patient flupirtin or a pharmaceutically acceptable salt thereof in an amount, calculated as a free base, of 5 mg/kg, and a pharmaceutically acceptable salt of morphine in an amount, calculated as a free base, of 2.5 mg/kg to 10 mg/kg, wherein the analgesic effectiveness of the morphine is preserved, and wherein potential in the patient for development of dependence on, and tolerance to, the morphine is reduced.

2. Use of flupirtin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable salt of morphine, in the manufacture of a medicament formulated to deliver to a patient the flupirtin, or the pharmaceutically acceptable salt thereof, in an amount, calculated as a free base, of 5 mg/kg, and the pharmaceutically acceptable salt of morphine in an amount, calculated as a free base, of 2.5 mg/kg to 10 mg/kg, wherein the analgesic effectiveness of the morphine is preserved, and wherein potential in the patient for development of dependence on, and tolerance to, the morphine is reduced.

Figure 1

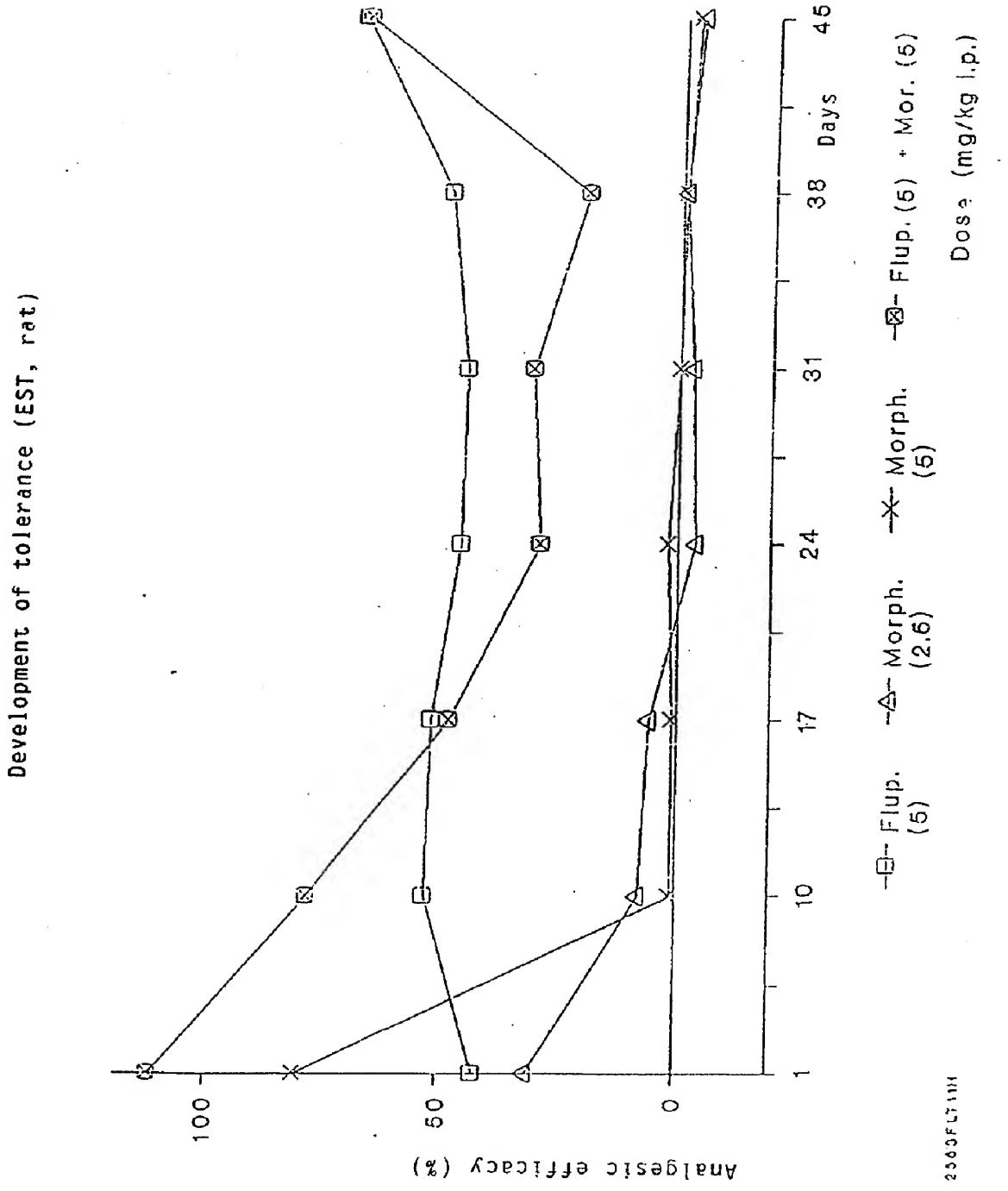
Development of tolerance (EST, rat)
Analgesic efficacy (%)
100
50
0
1
10
17
24
31
38
45
Days
Flup. (5)
Morph. (2,6)
Morph. (5)
Flup.(5) + Mor. (5)
Dose (mg/kg i.p.)

Figure 2

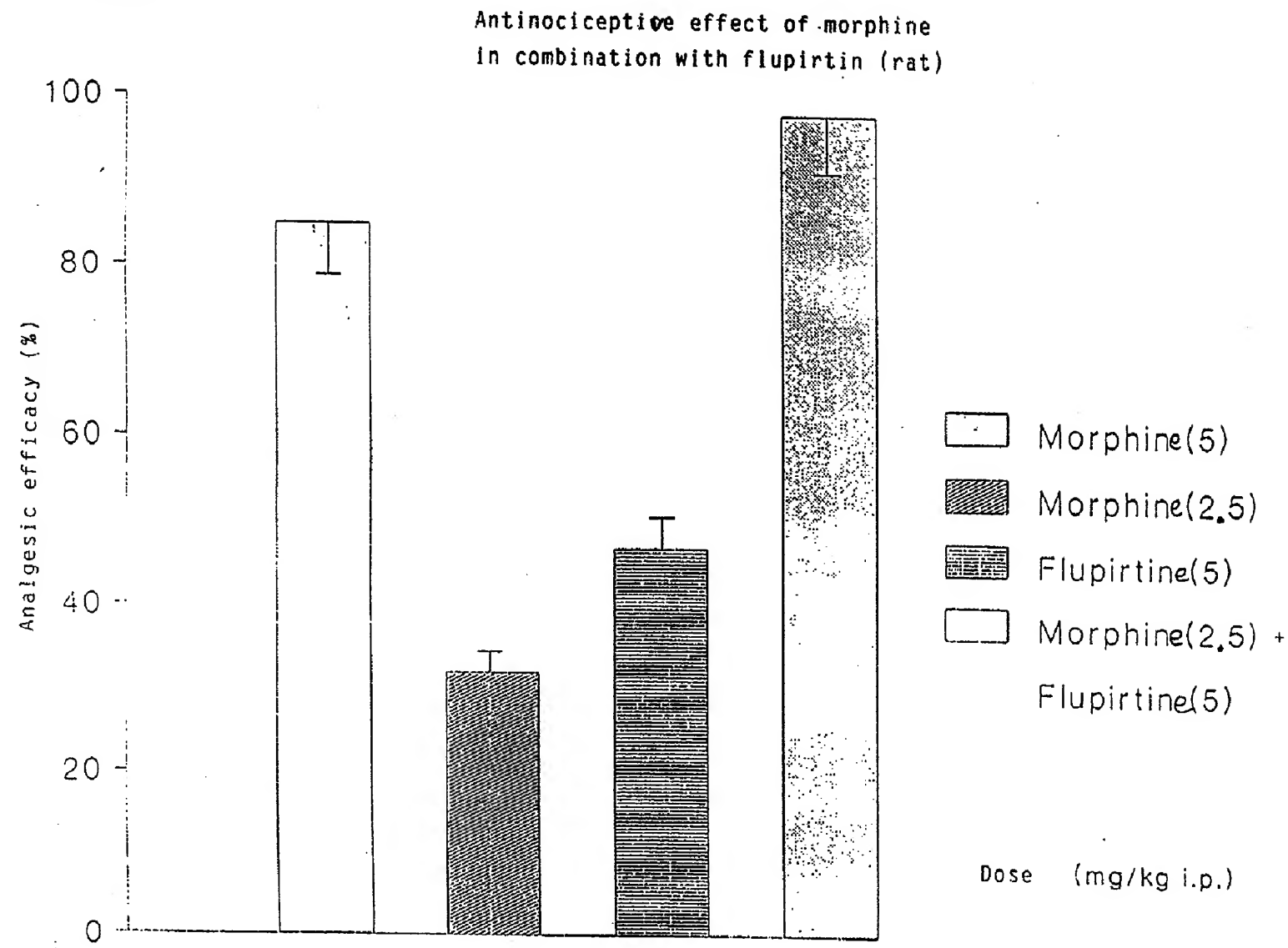

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Figure 3

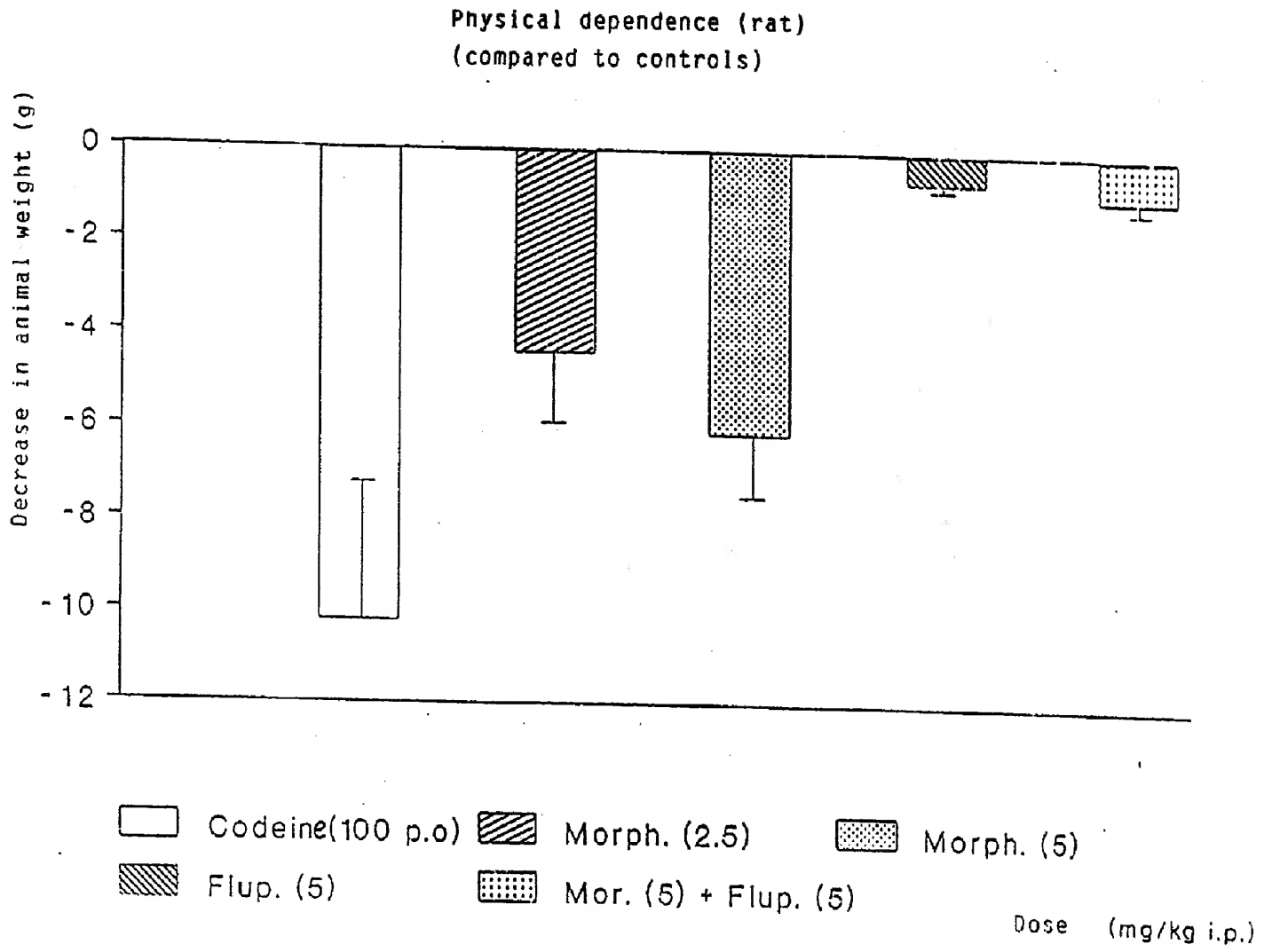

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Figure 4

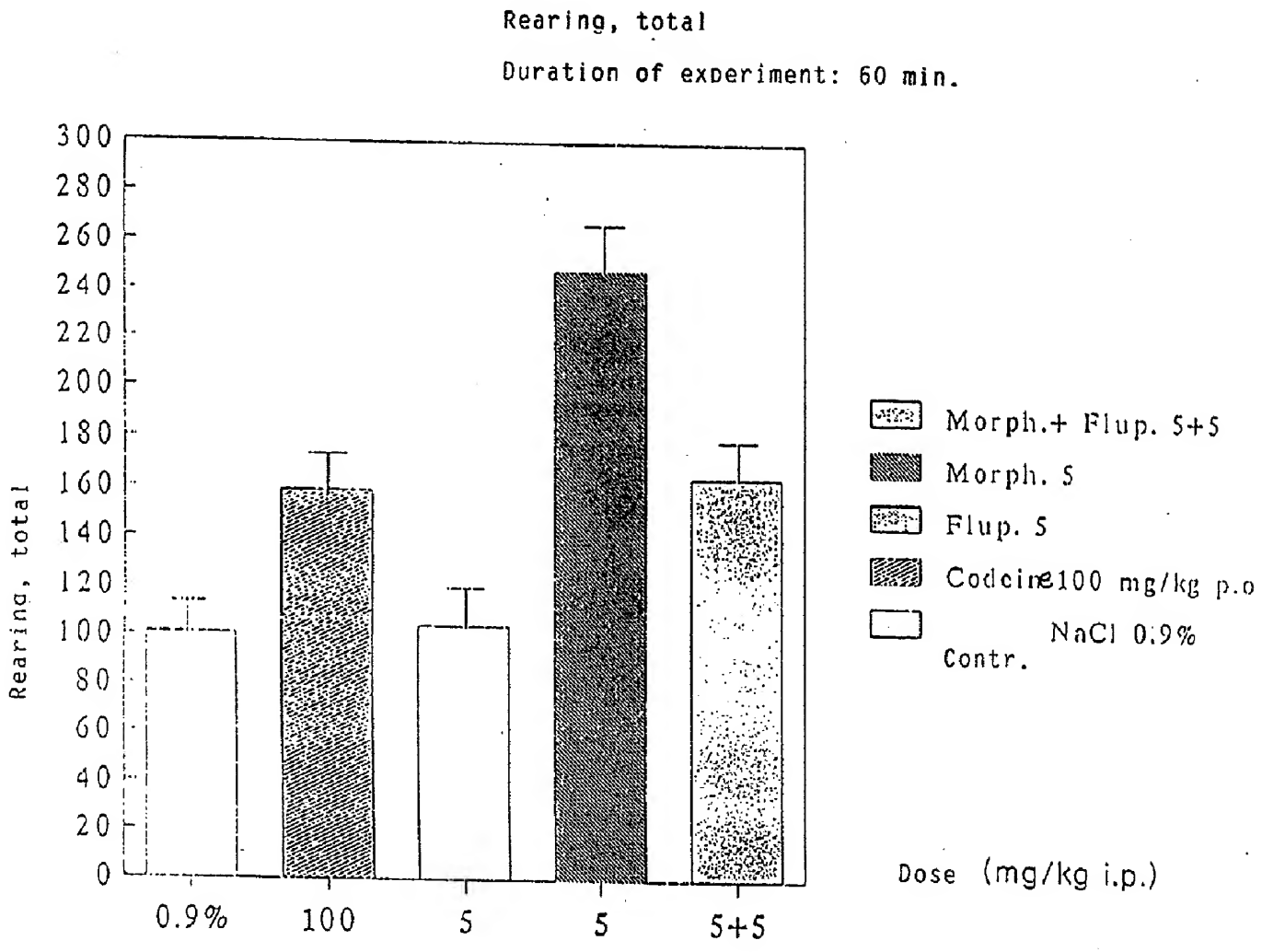

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Figure 5

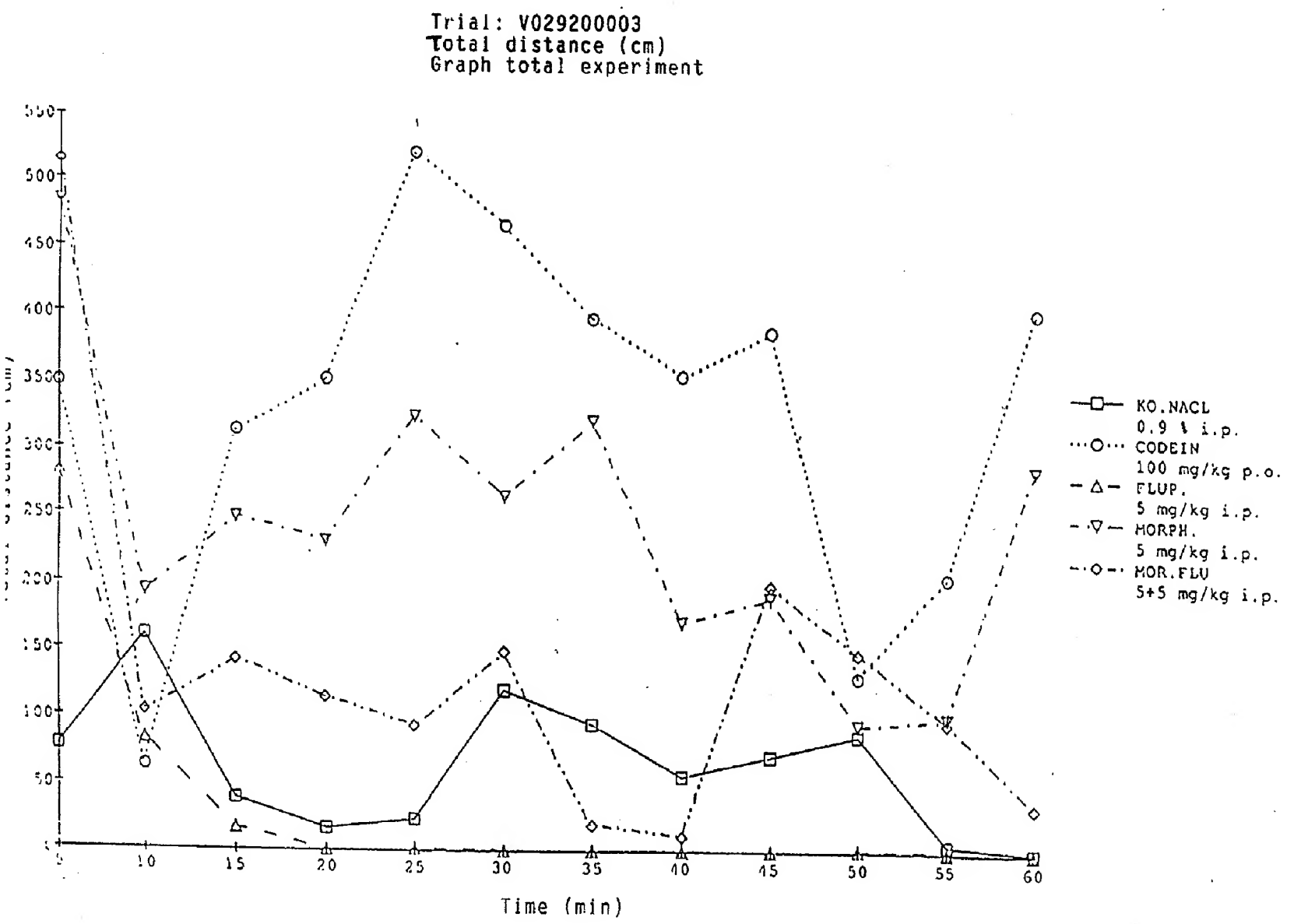

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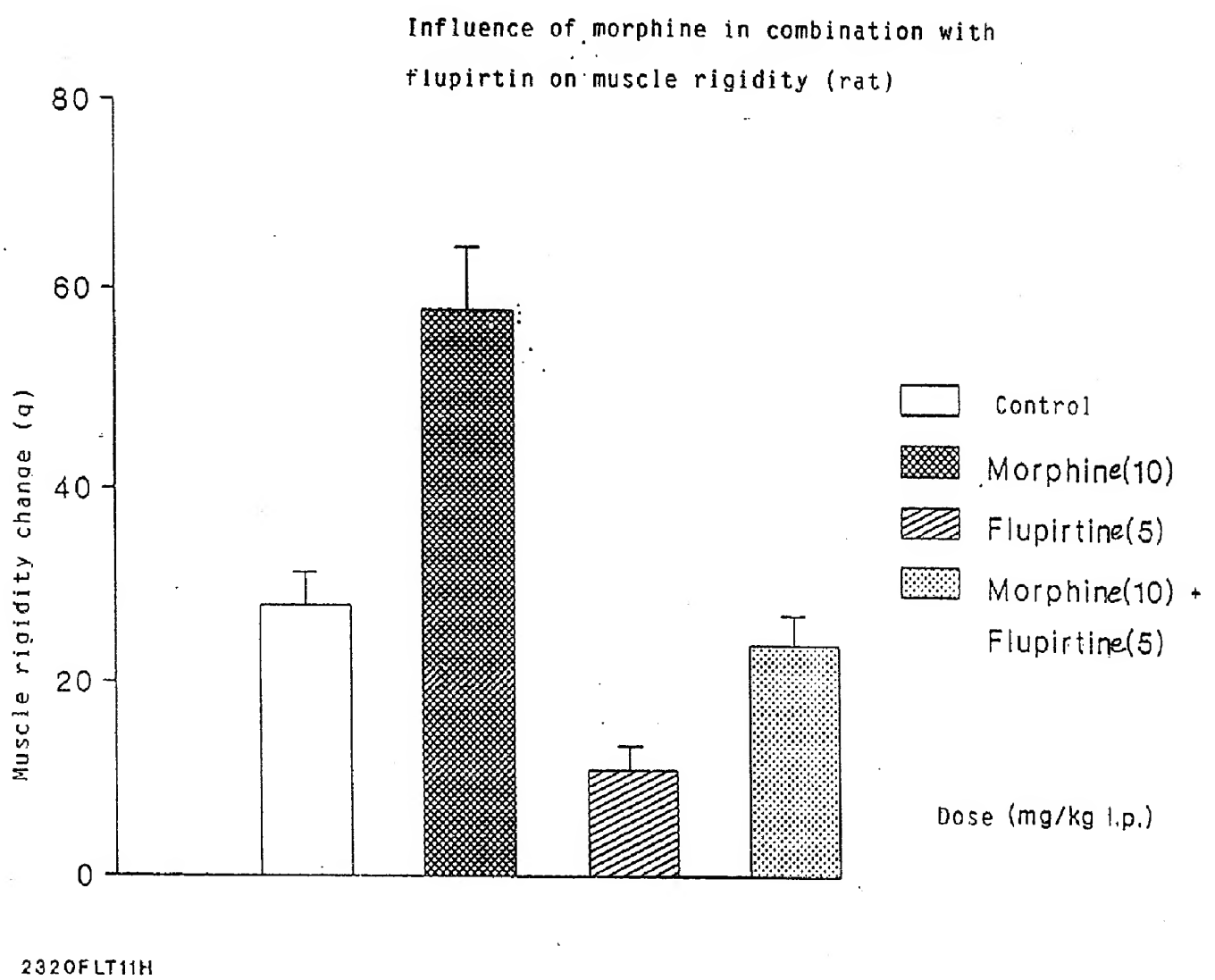
Figure 6



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